

## HAIR GROWTH PROMOTER

The present invention relates to an agent for promoting the growth of hair and/or decreasing hair fall-out, containing particular cyclic compounds, and to a method for decreasing hair fall-out and for promoting hair growth.

The human scalp normally harbors 100,000 to 150,000 hair follicles or hairs. The hair follicles or hair roots or hair bulbi are the hair-forming organs. The long, strong hairs, which build up the hair coverage of the head, are referred to as terminal hairs. The very fine, very short hairs, barely protruding over the surface of the skin, at the edges of the head of hair coverage or on the forehead, are referred to as fuzz hair or as vellus hair. The growth of hair is not continuous, but cyclical. Three growth phases are identified: (1) the anagen, during which the hair grows, (2) the katagen, during which the hair follicle prepares for the next phase, the telogen, and the previously growing hair is converted into a resting hair or club hair and (3) the telogen, that is, the resting phase, during which hair growth ceases completely. In response to a signal, which is not identified at the present time, the telogen follicle awakens to a new activity or commences a new anagen, in the course of which a new hair grows and the existing club hair is shed. This hair growth cycle proceeds unchanged during the whole of life and, moreover equally in the case of the long, strong terminal hair as well as in the case of the very short fuzz hair or vellus hair. A prerequisite for a normal growth of a healthy head of hair is a perfectly functioning organism and an optimum supply for it of all the necessary nutrients and auxiliary materials. Many factors can affect the growth of the hair on the head, namely wrong nutrition, deficient nutrition, severe illnesses, medicinal drugs, emotional stresses and temporary disorders of the hormone balance in the organism. A loss of hair, brought about by such factors, usually is temporary.

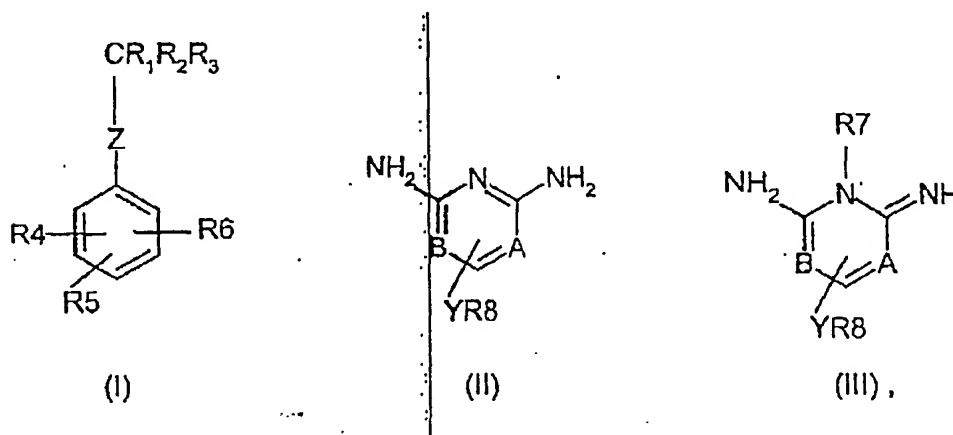
The form of the hair, the terminal hair or the fuzz hair, or also the hair forms, which lie between the terminal hair and the fuzz hair, which form the hair follicles in the course of life, depends to a large degree on the genetic disposition or the hereditary factors inherent in the hair follicles, as well as on the male sexual hormones. In persons with the hereditary factors to male or androgenic loss of hair, the terminal hair follicles in the scalp commence to change over into vellus hair follicles in the course of puberty. This conversion process can proceed to very different extents, resulting in scalp regions, which are partially, predominantly or completely covered with fuzz hair follicles or fuzz hair, or partially have the androgenic baldness of the male type (male baldness). The male loss of hair is an irreversible form of the loss of hair, unless means are found, which could retard, stop or reverse the transformation of terminal hair follicles into fuzz hair follicles or, in the latter case, transform fuzz hair follicles back into terminal hair follicles.

In the literature, materials, such as Minoxidil, the 5-alpha-reductase inhibitor Finasterid (propecia) have been described repeatedly and are said to retard or, to a limited extent, stop or also reverse the conversion of terminal hair follicles into fuzz hair follicles. Admittedly, Minoxidil, an antihypertensive drug, when administered perorally, promotes on the greater part of the skin to a very pronounced extent the conversion of fuzz hair follicles into terminal hair follicles; however, on the scalp, the corresponding effect is only very weak and from cosmetic points of view, of only a very limited extent, this state of affairs practically being unchanged when the Minoxidil is applied epicutaneously on the scalp. Admittedly, Finasterid, when administered perorally, is able to inhibit, stop or reverse the transformation of terminal hair follicles into vellus hair follicles to a limited extent. However, from cosmetics points of view, this effect is also not satisfactory from every point of view.

Since far more than half the men and, to an increasing extent, also women are affected by loss of hair, there is a great demand for materials, which are able to inhibit, stop or even reverse hair falling out, especially in men, in all its outward appearances.

Surprisingly, it has now been found that certain benzene derivatives of formula (I) and heteroaromatic compounds of formula (II), alone or in combination with one another, applied epicutaneously on the scalp, can decisively improve the hair falling out phenomenon especially in men, the conversion of terminal hair follicles into vellus hair follicles being retarded, stopped or even reversed.

The object of the present invention therefore is an agent for promoting the growth of hair and/or decreasing the falling out of hair with a content of at least one of the compounds of formula (I), (II) and/or (III) or their physiologically tolerated salts,



in which the groups A, B, Y, Z and R1 to R8 independently of one another have the following meaning:

A and B independently of one another represent a CH group or a nitrogen atom, at least one of the two groups A and B representing a CH group,

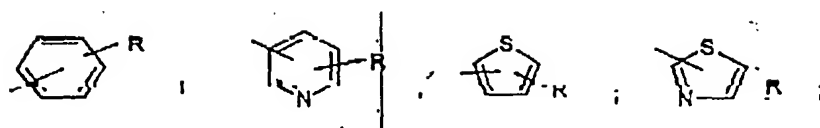
Y represents -O-,  $-(CH_2)_n-$ , -NH-CH<sub>2</sub>-, -CH<sub>2</sub>-NH-, -NH-CH<sub>2</sub>-, -N=N-, -CH=CH-, -CH<sub>2</sub>-O-, O-CH<sub>2</sub>-, -N=CH-, -CH=N-,  $-(CH_2-CH_2-O)_m-$  or  $-(O-CH_2-CH_2)_m-$ , with m and n equal to a whole number from 1 to 4,

Z represents -NH-CH<sub>2</sub>-, -CH<sub>2</sub>-CH<sub>2</sub>-, -CH=CH- or -CH<sub>2</sub>-NH-,

R1 is -H, -OH or a C<sub>1</sub> to C<sub>4</sub> hydroxyalkyl group,

R2 is H, cyclopropyl or a C<sub>1</sub> to C<sub>4</sub> alkyl group,

R3 is a C<sub>1</sub> to C<sub>2</sub> hydroxyalkyl group, -CH<sub>2</sub>-X or -CHX<sub>2</sub> (with X = F, Cl, Br or I), -COCH<sub>3</sub>, -CF<sub>3</sub>, -CH<sub>3</sub> or



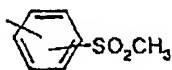
(in which R is  $\text{NO}_2$ ,  $\text{SO}_2\text{CH}_3$ ,  $\text{CF}_3$ ,  $\text{CHF}_2$ , F, Cl),

R4, R5, R6 independently of one another are  $-\text{NO}_2$ ,  $-\text{CF}_3$ ,  $-\text{CHF}_2$ ,  $-\text{F}$ ,  $-\text{Cl}$ ,  $-\text{Br}$  or  $-\text{H}$ ,

R7 is  $\text{OH}$ ,  $-\text{OSO}_3\text{H}$ ,  $-\text{O}-(\text{C}_1 \text{ to } \text{C}_4 \text{ alkyl})$  or  $-\text{OCOCH}_3$ ,

R8 is a  $\text{C}_1$  to  $\text{C}_6$  alkyl group, a  $\text{C}_1$  to  $\text{C}_6$  hydroxyalkyl group, a  $\text{C}_2$  to  $\text{C}_6$  hydroxyalkenyl group, an aryl group, a heteroaryl group or a  $\text{C}_2$  to  $\text{C}_6$  alkenyl carboxylic acid group.

Preferred are compounds of formula (1) in which Z is  $-\text{NH}-\text{CH}_2-$ ,  $-\text{CH}_2-\text{CH}_2-$ ,  $-\text{CH}=\text{CH}-$  or  $-\text{CH}_2-\text{NH}-$ , R1 is  $-\text{OH}$ ,  $-\text{CH}_2\text{OH}$  or  $-\text{CH}_2\text{CH}_2\text{OH}$ , R2 is  $-\text{H}$ ,  $-\text{CH}_3$ , or  $-\text{C}_2\text{H}_5$ ; R3 is



$\text{C}_1$  to  $\text{C}_2$  hydroxyalkyl group,  $-\text{CH}_2-\text{X}$  (with  $\text{X} = \text{F}, \text{Cl}, \text{Br}$  or  $\text{I}$ ),  $-\text{CF}_3$  or  $-\text{CH}_3$  and R4, R5, R6 independently of one another are  $-\text{NO}_2$ ,  $-\text{CF}_3$ ,  $-\text{CHF}_2$ ,  $-\text{CH}_2\text{F}$ ,  $-\text{F}$ ,  $-\text{Cl}$ ,  $-\text{Br}$  or  $-\text{H}$ ; compounds of formula (I), in which Z represents  $-\text{NH}-\text{CH}_2-$ ,  $-\text{CH}_2-\text{CH}_2-$ ,  $-\text{CH}=\text{CH}-$  or  $-\text{CH}_2-\text{NH}-$ , R1 represents  $-\text{OH}$  or  $-\text{CH}_2\text{OH}$ ; R2 represents  $-\text{H}$  or  $-\text{CH}_3$ , R3 represents a  $\text{C}_1$  to  $\text{C}_2$  hydroxyalkyl group,  $-\text{CH}_2-\text{X}$  (with  $\text{X} = \text{F}, \text{Cl}, \text{Br}$  or  $\text{I}$ ),  $-\text{CF}_3$  or  $-\text{CH}_3$  and, independently of one another, R4 represents  $-\text{NO}_2$ , R5 represents  $-\text{CF}_3$  and R6 represents  $-\text{H}$  and especially compounds of Formula (I) in which Z represents  $-\text{NH}-\text{CH}_2-$ , R1 represents  $-\text{OH}$ , R2 represents  $-\text{H}$ , R3 represents  $-\text{CH}_2\text{OH}$ , R4 represents  $-\text{NO}_2$ , R5 represents  $-\text{CF}_3$  and R6 represents  $-\text{H}$  are particularly preferred.

Also preferred are compounds of formula (II) in which A represents  $-\text{CH}-$  and B represents  $-\text{CH}-$  or  $-\text{N}$ , Y represents  $-\text{N}=\text{N}-$ ,  $-(\text{CH}_2)_n-$ ,  $-\text{CH}=\text{CH}$ ,  $-\text{CH}=\text{N}-$  or  $-\text{N}=\text{CH}-$  and R8 a  $\text{C}_1$  to  $\text{C}_6$  alkyl group, a  $\text{C}_1$  to  $\text{C}_6$  hydroxyalkyl group, a phenyl group, a benzyl group or a pyridyl group, compounds of formula (II) in which A and B represent

-CH-, Y represents -N=N- and R8 represents a pyridyl group, being particularly preferred.

Also preferred are compounds of formula (III) in which A is -CH- and B is -CH- or -N-, Y is -N=N-,  $-(CH_2)_n-$ , -CH=CH-, -CH=N- or N=CH-, R7 is -OH, -OSO<sub>3</sub>H or -O-(C<sub>1</sub> to C<sub>4</sub> alkyl) and R8 is a C<sub>1</sub> to C<sub>6</sub> alkyl group, a C<sub>1</sub> to C<sub>6</sub> hydroxyalkyl group, a phenyl group, a benzyl group or a pyridyl group, compounds of formula (III), in which A and B are -CH-, Y is -N=N-, R7 is -OH (including the corresponding tautomeric N-oxides) and R8 is a pyridyl group, being particularly preferred.

Especially preferred here are those agents, which contain one or more of the following compounds: 1-(N-(2'-nitro-4'-trifluoromethyl-phenyl)amino)-3-chloro-2-hydroxy-propane, 1-(N-(2'-nitro-4'-trifluoromethyl-phenyl)-amino)-2-hydroxy-2-trifluoromethyl-ethane, 1-(N-(2'-nitro-4'-trifluoromethyl-phenyl)-amino)-2,3-dihydroxypropane, 1-(2'-nitro-4'-trifluoromethyl-phenyl)-3,4-dihydroxy-1-butene, 2,6-diamino-3-((pyridine-3-yl)-azo)-pyridine and 2,6-diamino-3-((pyridine-3-yl)-azo)-pyridine-1-oxide. Of these compounds, especially 1-(N-(2'-nitro-4'-trifluoromethyl-phenyl)-amino)-2,3-propylene glycol and 2,6-diamino-3-((pyridine-3-yl)-azo)-pyridine and combinations of these compounds are named.

The inventive cosmetic agent, containing at least one compound of formulas (I), (II) and/or (III), may exist in any form suitable for application on hair and the scalp, especially in the form of an aqueous, alcoholic or aqueous alcoholic preparation, such as a solution, gel, cream, emulsion or dispersion. It is also possible to dispense these agents as a spray or a foam from a pressurized container with conventional blowing agents, which are liquefied under pressure, for example, chlorofluoroalkanes such as CCl<sub>3</sub>F, CCl<sub>2</sub>F<sub>2</sub>, C<sub>2</sub>Cl<sub>3</sub>F<sub>3</sub>, CCl<sub>2</sub>F<sub>2</sub>, CHCl<sub>2</sub>F and (CClF<sub>2</sub>)<sub>2</sub>, highly volatile hydrocarbons, such as n-butane and n-propane, or also dimethyl ether, carbon dioxide, nitrous oxide, nitrogen, methylene chloride and 1,1,1-trichloromethane.

The forms, in which the inventive, cosmetic agents are prepared, may also, in particular, be those, which remain on the hair and the scalp for a longer period of time and comprise, for example, insertion materials, combing gels, hair pomades, hair treatments, hair oils and hair tonics. Especially preferred in this connection are hair tonics as well as so-called "sustained release" preparations, which emit the active ingredient uniformly over a longer period of time or production of the compounds of formulas (I) and (II) as liposomes.

The total content of compounds of formula (I) and/or (II) in the inventive agent preferably is about 0.001 to 10 percent by weight, an amount of 0.05 to 3 percent by weight being particularly preferred.

The composition of the inventive cosmetic agent represents a mixture of the compounds of formulas (I) and/or (II) with components, which are customary for such agents, such as carriers and additives.

As carriers, in general those materials come into consideration, which increase the percutaneous absorption of the active ingredients, do not disadvantageously affect the active ingredient components and, at the same time, are harmless with respect to the human skin. Such carrier materials are, for example, water, low molecular weight aliphatic alcohols, such as ethanol, propanol and isopropanol, as well as mixtures of these materials. However, mixtures of the aforementioned compounds with 1 to 30 percent by weight of 1,2-propylene glycol are also advantageous.

The following come into consideration as conventional additives in the inventive cosmetic agents: carrier compounds or penetration accelerators, such as benzyl alcohol, 2-benzyl-oxyethanol,  $\alpha$ -hydroxycarboxylate esters, vanillin, p-hydroxyanisole, 3-hydroxy-4-methoxy-benzaldehyde, 2-phenoxyethanol, salicylaldehyde, 3,5-dihydroxybenzaldehyde, 3,4-dihydroxybenzaldehyde, 4-hydroxy-phenylacetamide, methyl p-hydroxybenzoate, p-hydroxy-benzaldehyde, m-cresol, hydroquinone

monomethyl ether, o-fluorophenol, m-fluorophenol, p-fluorophenol-2-(2'-hydroxyphenoxy)-ethanol, 3,4-methylene-dioxy-phenol, resorcinol monomethyl ether, 3,4-dimethoxy-phenol, 3-trifluoromethyl-phenol, resorcinol monoacetate, ethylvanillin, 2-thiophenethanol, butyl lactate and butyl glycolate; thickeners, such as kaolin, bentonite, fatty acids, higher fatty alcohols, starch, polyacrylic acid, cellulose derivatives, alginates, Vaseline or paraffin oil; compounds from the classes of the anionic, cationic, amphoteric, zwitterionic or nonionic surfactants or surface active agents, such as fatty alcohol sulfates, alkyl sulfonates, alkylbenzene sulfates, quaternary ammonium salts, alkyl betaines and ethoxylated esters of fatty acids; furthermore, opacifiers, such as polyethylene glycol esters, foam stabilizers, sequestering agents, buffers, preservatives, solubilizers, perfume oils, natural or synthetic cosmetic polymers, such as cellulose derivatives, shellac, pectins, polyvinylpyrrolidone, polyvinyl acetate, polyacrylic compounds, such as acrylic acid or methacrylic acid polymers, basic polymers of esters of acrylic acid or methacrylic acid with aminealcohols, polyacrylonitrile and chitosan derivatives, hair conditioners, active ingredients against dandruff, plant extracts as well as hair-care components, such as protein hydrolysates, lanolin derivatives, cholesterol, pantothenic acid or betaine.

Of course, the inventive agents may contain additional, known active ingredients, which maintain a healthy growth of hair and/or support or promote the recuperation of hair growth in the case of disorders of a physiological or non-physiological kind, such as Minoxidil, diazoxide, cyclosporin A, diphenylhydantoin, acetazolamide, antiandrogens of a steroidal and nonsteroidal type, such as cyproterone acetate, oxendolone, spiro lactone, 5-alpha-reductase inhibitors, selected extracts of natural origin, retinoids, estrogens, vitamins, such as biotin, trace elements, neuropeptides, nutrients, especially of the essential type, cytokins, neurotrophins, neutrophin receptor antagonists, antimicrobial substances, steroidal or non-steroidal anti-inflammatory substances, calcium antagonists or potassium channel openers (potassium channel agonists).

The present invention furthermore relates to a method for treating hair to reduce hair fall-out and promote hair growth, wherein a sufficient amount of the previously described inventive agent, containing at least one compound of formula (I) or (II), in general about 1 to 30 milliliter and preferably 2 to 15 milliliter, is applied on the hair and scalp, the scalp is massaged subsequently preferably for about 1 to 5 minutes, and the agent is left on the hair and the scalp for prolonged period of time, preferably for at least 24 hours.

Preferably, the treatment is carried out once or twice daily and for a period of 3 to 24 months. Optionally, the interval between applications can then be increased.

A further object of the present invention is the use of compounds of formulas (I), (II) and/or (III), alone or in combination with one another, to promote hair growth and/or to decrease androgenic loss of hair. The use of one or more compounds from the group consisting of 1-(N-(2'-nitro-4'-trifluoromethyl-phenyl)-amino)-3-chloro-2-hydroxy-propane, 1-(N-(2'-nitro-4'-trifluoromethyl-phenyl)-amino)-2-hydroxy-2-trifluoromethylethane, 1-(N-(2'-nitro-4'-trifluoromethyl-phenyl)-amino)-2,3-propylene glycol, 1-(2'-nitro-4'-trifluoro-methyl-phenyl)-3,4-dihydroxy-1-butene, 2,6-diamino-3-((pyridine-3-yl)-azo)-pyridine and 2,6-diamino-3-((pyridine-3-yl)-azo)-pyridine-1-oxide. Of these compounds, especially 1-(N-(2'-nitro-4'-trifluoromethyl-phenyl)-amino)-2,3-propylene glycol and 2,6-diamino-3-((pyridine-3-yl)-azo)-pyridine is particularly preferred for promoting hair growth and/or decreasing androgenic loss of hair.

The invention is explained in greater detail by means of the following examples, without being limited to these.

### Examples

#### Example 1: Hair Tonic

1.0 g 1-(N-(2'-nitro-4'-trifluoromethyl-phenyl)-amino)-2,3-propylene glycol



1.0 g	2,6 diamino-3-((pyridine-3-yl)-azo)-pyridine
3.0 g	1,2-propylene glycol
0.3 g	perfume oil
to 100.0 g	ethanol (96%)

In each case, 15 milliliters of the above hair tonic are applied once daily (every 24 hours) on the hair and the scalp and massaged into the scalp for 1 minute.

#### **Example 2: Hair Tonic**

2.0 g	1-(N-(2'-nitro-4'-trifluoromethyl-phenyl)-amino)-2,3-propylene glycol
1.0 g	2,6 diamino-3-((pyridine-3-yl)-azo)-pyridine
0.1 g	menthol
0.3 g	perfume oil
to 100.0 g	ethanol (96%)

The above hair tonic is applied twice daily on the hair and the scalp and massaged into the scalp for 2 minutes.

#### **Example 3: Hair Tonic**

0.30 g	1-(N-(2'-nitro-4'-trifluoromethyl-phenyl)-amino)-2,3-propylene glycol
0.05g	polyvinylpyrrolidone
0.10 g	Arnika tincture
0.30 g	perfume oil
to 100.00 g	ethanol (96%)

The above hair tonic (in each case 10 milliliters) is applied twice daily on the hair and the scalp and massaged into the scalp for 2 minutes.

**Example 4: Hair Tonic**

1.0 g	1-(N-(2'-nitro-4'-trifluoromethyl-phenyl)-amino)-2,3-propylene glycol
0.5 g	2,6 diamino-3-((pyridine-3-yl)-azo)-pyridine
0.2 g	hydrogenated castor oil with 60 moles of ethylene oxide (Chremophor RH 60 of BASF AG/Ludwigshafen)
0.3 g	perfume oil
40.0 g	ethanol (96%)
to 100.0 g	water

The above hair tonic (in each case 20 milliliters) is applied once daily on the hair and the scalp and massaged into the scalp for 1 to 2 minutes.

**Example 5: Hair Treatment**

0.4 g	1-(N-(2'-nitro-4'-trifluoromethyl-phenyl)-amino)-2,3-propylene glycol
0.2 g	hydrogenated castor oil with 60 moles of ethylene oxide (Chremophor RH 60 of BASF AG/Ludwigshafen)
0.3 g	perfume oil
0.5 g	cetyl alcohol
to 100.0 g	water

The above hair treatment (in each case 15 milliliters) is applied once daily on the hair and the scalp and massaged into the scalp for 2 minutes. After a period of action of about 24 hours, the hair treatment is rinsed out with lukewarm water.

**Example 6: Hair Tonic**

1.0 g	1-(N-(2'-nitro-4'-trifluoromethyl-phenyl)-amino)-3-chloro-2-hydroxy-propane
1.0 g	2,6 diamino-3-((pyridine-3-yl)-azo)-pyridine
3.0 g	1,2-propylene glycol
0.3 g	perfume oil
to 100.0 g	ethanol (96%)

In each case, 15 milliliters of the above hair tonic are applied once daily (every 24 hours) on the hair and the scalp and massaged into the scalp for 1 minute.

**Example 7: Hair Tonic**

2.0 g	1-(N-(2'-nitro-4'-trifluoromethyl-phenyl)-amino)-2-hydroxy-2-trifluoromethylethane
1.0 g	2,6 diamino-3-((pyridine-3-yl)-azo)-pyridine
0.1 g	menthol
0.3 g	perfume oil
to 100.0 g	ethanol (96%)

The above hair tonic is applied twice daily on the hair and the scalp and massaged into the scalp for 2 minutes.

**Example 8: Hair Tonic**

0.30 g	1-(N-(2'-nitro-4'-trifluoromethyl-phenyl)-amino)-1-butene-3,4-diol
0.05 g	polyvinylpyrrolidone
0.10 g	Arnika tincture
0.3 g	perfume oil
to 100.0 g	ethanol (96%)

The above hair tonic (in each case 10 milliliters) is applied twice daily on the hair and the scalp and massaged into the scalp for 2 minute.

**Example 9: Hair Tonic**

0.7 g	1-(N-(2'-nitro-4'-trifluoromethyl-phenyl)-amino)-2,3-propylene glycol
0.9 g	2,6 diamino-3-((pyridine-3-yl)-azo)-pyridine-1-oxide
0.2 g	hydrogenated castor oil with 60 moles of ethylene oxide (Chremophor RH 60 of BASF AG/Ludwigshafen
0.3 g	perfume oil
50.0 g	ethanol (96%)
to 100.0 g	water

The above hair tonic (in each case 20 milliliters) is applied once daily on the hair and the scalp and massaged into the scalp for 1 to 2 minute.

**Example 10: Hair Treatment**

0.3 g	1-(N-(2'-nitro-4'-trifluoromethyl-phenyl)-amino)-2,3-propylene glycol
0.01 g	2,6 diamino-3-((pyridine-3-yl)-azo)-pyridine-1-oxide
0.2 g	hydrogenated castor oil with 60 moles of ethylene oxide (Chremophor RH 60 of BASF AG/Ludwigshafen
0.3 g	perfume oil
0.5 g	cetyl alcohol
to 100.0 g	ethanol (96%)

The above hair treatment (in each case 15 milliliters) is applied once daily on the hair and the scalp and massaged into the scalp for 2 minutes. After a period of action of about 24 hours, the hair treatment is rinsed out with lukewarm water.

### Example 11: Hair Growth Emulsion

0.4 g	1-(N-(2'-nitro-4'-trifluoromethyl-phenyl)-amino)-2,3-propylene glycol
0.1 g	2,6 diamino-3-((pyridine-3-yl)-azo)-pyridine
30.0 g	partially hydrogenated peanut oil (oleum arachidis hydrogenatum)
5.0 g	cetyl stearyl alcohol
0.2 g	perfume oil
10.0 g	propylene glycol
to 100.0 g	water

The above hair growth agent (in each case 20 milliliters) is applied once daily on the hair and the scalp and massaged into the scalp for 1 to 2 minute. After a period of action of about 24 hours, the agent is rinsed out with lukewarm water.

### Example 12: Hair Growth Gel

0.300 g	1-(N-(2'-nitro-4'-trifluoromethyl-phenyl)-amino)-2,3-propylene glycol
0.560 g	carboxyvinyl polymer (Carbopol 940 of BF Goodrich/USA)
0.224 g	sodium hydroxide
to 100.000 g	water

The above hair growth agent (in each case 15 milliliters) is applied once daily on the hair and the scalp and massaged into the scalp for 2 minutes. After a period of action of about 24 hours, the agent is rinsed out with lukewarm water.

Unless it is stated otherwise, all weight data is given as weight percent.